Title: A meta-analysis of peripheral tocopherol levels in age-related cognitive decline and Alzheimer's disease

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Abstract

Findings from observational studies and clinical trials on the associations between vitamin E and dementia remain controversial. Here we conducted a meta-analysis to determine the difference in blood tocopherols levels between patients with Alzheimer's disease (AD) or age-related poor cognitive function and healthy controls.

Standardised mean difference (SMD) and 95% confidence intervals (CIs) were calculated and entered into a random effects model. Study quality, heterogeneity and publication bias were also investigated.

Thirty-one articles were included in the meta-analysis, which included analyses for α-, β-, γ- and δ-tocopherols. These results indicated that individuals with AD or age-related cognitive deficits and mild cognitive impairment (MCI) had lower circulatory concentrations of α-tocophenol compared with healthy controls (AD: SMD = −0.97, 95% confidence interval [CI] = −1.27 to −0.68, Z = 6.45, P < 0.00001; age-related cognitive deficits and MCI: SMD = −0.72, 95% CI = −1.12 to −0.32, Z = −3., P < 0.0005). Levels of β-, γ- and δ-tocophenols did not significantly differ between groups of AD and age-related cognitive deficits compared to controls.

These results suggest that lower α-tocopherol levels have a strong association with AD and MCI supporting evidence for the role of diet and vitamin E in AD risk and age-related cognitive decline.

Keywords: Vitamin E; α-tocopherol; γ-tocopherol; dementia; MCI; meta-analysis

Introduction

Several studies have proposed different factors that may contribute to the risk of developing Alzheimer's disease (AD), including genetic and environmental factors such as exposure to pesticides, paints and glues, as well as lifestyle factors such as lack of exercise, smoking and alcohol consumption, and a diet lacking vegetables and fruit [1].

Dietary intake has been progressively examined as a potential independent risk factor of the age-related cognitive decline and dementia, and the intake of certain nutrients such as vitamin E have been implicated in healthy brain function, though results are conflicting [2,3]. Vitamin E is an essential dietary micronutrient comprising a group of structurally-related forms including four different tocopherols. α–tocopherol is the most bioavailable antioxidant isoform of vitamin E in the human body and most often used in supplements. Vitamin E is found in vegetable oils and products derived from vegetables whole grains, nuts and seeds, animal fats and meats, with variations in levels of tocopherols between food sources for examples while some oils, such as soybean oil, contain a mix of tocopherols, others, such as sunflower oil, contain almost exclusively α-tocopherol (*for further review see* [4]).

Tocopherols have antioxidant and anti-inflammatory properties. Interestingly, there are variations in antioxidant activity between tocopherols with some forms more effective than others at neutralizing some free radicals. Each form also has unique biological functions, linked to variations in immune activity, hypocholesterolemic properties and modulation of different signalling pathways (for review see [5]). Considering the large numbers of studies showing the crucial role of oxidative stress in the development of neurodegenerative disorders (for review see [6]), levels of antioxidants and their supplements have been proposed as preventive measures against dementia. Though, experimental studies indicate that vitamin E exerts beneficial effects in animal models (for review see [7]), its efficacy in AD patients is controversial. For example, one of the earliest double-blind, randomized multicenter clinical trials [8] showed vitamin E slowed AD progression, though several subsequent double-blind study studies such as [9] found vitamin E supplementation had no benefit (for review see [10]). Two recent Cochrane reviews [11,12] were also unable to support evidence for the role of vitamin E supplementation, concluding that the amount and quality of research evidence was limited.

Results from studies investigating serum levels of tocopherols in dementia and mild cognitive impairment (MCI) have again, been contentious. For example Iuliano and colleagues [13] found no significant difference in serum α–tocopherol between patients with AD and age-matched controls while Mangialasche and colleagues [14] suggested that low levels were associated with increased risk of AD. Other studies have also led to conflicting conclusions regarding MCI and age-related cognitive decline [15]. Two meta-analyses on α–tocopherol and AD [16,17] did not find significant differences, however they both focussed only on AD and not MCI, and only on α-tocopherol. They also did not account for variations in measurement of tocopherols, particularly whether some studies controlled for cholesterol and were relatively restricted in the numbers of studies included in the analyses. Importantly, there are also numerous other associated risk factors, such as increasing age, female gender, and APOE4 genotype, as well as other variables implicated in some studies, such as family history of Alzheimer disease, depression, low educational level, smoking, diabetes, obesity, hypertension, and fatty diet (for review see [18]).

Thus, the aim of this study was to conduct a meta-analysis examining current literature regarding levels of different tocopherols in case-control studies for AD and MCI accounting for differences in variations in how levels of tocopherols were measured and discussing diagnostic criteria, inclusion criteria and possible influence of diet and medications.

Methods

This meta-analysis was performed in accordance to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement [19] to answer the following question: do blood levels of α-, γ-, β- or δ-tocopherol differ between individuals with AD or MCI, compared with age-matched controls?

Search strategy

We searched the Scopus, PubMed, Science Direct and Google Scholar databases up to 9th April 2019. When available, search terms were limited to those reported in the English language and to journal articles which consisted of ("tocopherol" OR "Vitamin E") AND (“dementia” OR "cognitive" OR “Alzheimer’s”). In addition, we evaluated the reference lists of the identified articles to identify relevant studies.

Inclusion and exclusion criteria

All the studies included in this meta-analysis abided by the following criteria. (1) Study design: case-control or cross-sectional. (2) Measure: α-, β-, γ- or δ-tocopherol blood levels. (3) Subjects: comprehensive assessment tools for dementia, AD and MCI. (4) Statistical analysis: studies contained mean serum or plasma levels of tocopherols together with standard deviations (SDs) or had other data that could be converted to mean SD (*See the Data Extraction section below*). (5) Methodological: studies measuring serum levels use high performance liquid chromatography (HPLC) in either serum or plasma.

Data extraction

Data and characteristics extracted from each study included: study design, location, number of subjects, age, percentage of females, assessment of dementia, assessment of tocopherol levels and their levels. As lipophylic α-tocopherol is carried in lipoprotein, its concentration is highly dependent on the level of plasma lipid. Thus, it has been proposed that vitamin E evaluation in plasma requires lipid standardization, specially total cholesterol (TC) [20]. We therefore took measures controlled for TC if available. To convert mean and 95% CI data in Sinclair *et al.* 1998 study [21] to SD the length of the confidence interval was divided by 3.92 and multiplied by the square root of the sample size. Median and interquartile range (IQR) data from the Foy *et al.* 1999 study [22] was converted to mean and SD using the formula described [23,24] and SE data from the Feillet-Coudray *et al.* 1999 [25,26] and Battino *et al.* 1997 studies [25,26] were converted to SD by dividing by the square root of the samples size.

Quality assessment

We developed a scale to assess the quality of selected studies for validation of the cases and healthy controls and, whether the individuals were excluded if they had other diseases, alcohol addiction, smoked, took recreational drugs and vitamin supplements. Studies were also assessed if they controlled for BMI, abnormal diets or malnutrition, and if there were variations in age between the groups or did not contain equal genders. Finally, studies were checked whether serum was collected in the morning following fasting. Using these criteria, the included studies within this meta-analysis were graded for their quality and bias to identifying any reasons for possible heterogeneity (**Supplementary Table 1**). The checklist was followed and the publications were graded.

Statistical analysis

Meta-analyses were performed using the Review Manager 5.3 software by using random effect models throughout. Results were reported as standardised mean differences (SMD), heterogeneity measured using I^2 and publication bias through visual inspection of funnel plots.

Results

Study selection

The search strategy returned 515 records for which titles and abstracts were screened. Out of the 81 full-text journal articles that were assessed for eligibility, 33 were retained for methodological quality checks and included in this meta-analysis. These divided into 29 studies that examined blood levels of tocopherols in AD and 14 studies that tested samples from MCI or age-related cognitive defects – some studies tested both groups and multiple tocopherols (**Figure 1**).

Study characteristics

Most studies reported male and female participants together, except one study reported effects for separate sexes [27]. The majority of studies were case-control, while nine were cross-sectional [14,15,27–33].

A number of the studies reported raw serum values tocopherols [25,28,30,34–42] either as μmol/l, μg/l while the other studies controlled for TC reporting values as μmol/mmol cholesterol.

α-tocopherol and AD and MCI

Results from the meta-analysis indicate that AD patients have a lower concentration of peripheral α-tocopherol compared with healthy age-matched controls (SMD = −0.97 μmol/L, 95% CI −1.27 to −0.68; Z = 6.45, P < 0.00001) (**Figure 2**). There was heterogeneity amongst the serum level trials (Heterogeneity $Tau^2 = 0.59$; $Chi^2 = 425.15$, df=29 (p<0.00001); I^2 =93%). Subgroup analysis of only studies that controlled for cholesterol reduced heterogeneity ($Tau^2 = 0.18$; Chi^2 =65.13, df=10 (p<0.00001); I^2 =85%) while overall effect still remained significant (Z = 2.56, P < 0.01).

Publication bias was not detected and sensitivity analysis performed by omitting each study, and calculating the pooled SMD again for the remaining studies indicated the results were stable.

Serum levels of α-tocopherol were also significantly lower in age-related poor cognitive performance and MCI (SMD = −0.72, 95% CI −1.12 to −0.28; Z = 3.51, P < 0.0005) (**Figure 3**). Again, there was heterogeneity amongst the studies (Heterogeneity Tau^2 = 0.54; Chi^2 = 457.42, df=13 (p<0.00001); I^2 =97%), that was reduced when only including studies that controlled for cholesterol (Heterogeneity Tau^2 = 0.06; Chi^2 = 28.26, df=7 (p<0.0002); 1^2 =75%) while significance remained (Z=2.06, P=0.04).

γ-tocopherol and AD and MCI

Results from the meta-analysis indicate no differences in serum concentrations of serum γ-tocopherol between AD cases and healthy age-matched controls (SMD = −0.14, 95% CI −0.83 to −0.55; Z = 0.41, P =0.69) (**Figure 4**). There was heterogeneity amongst the serum level trials (Heterogeneity Tau^2 = 0.48; Chi^2 = 99.79, df=3 (p<0.00001); 1^2 =97%).

Serum levels of γ-tocopherol were also not significantly different in MCI and age-related poor cognitive performance and MCI (SMD = −0.17, 95% CI −0.39 to −0.05; Z = 1.47, P = 0.14) (**Figure 5**). There was heterogeneity amongst the serum level trials (Heterogeneity Tau^2 = 0.05; Chi^2 = 34.04, df=4 (p<0.00001); 1^2 =88%).

β-tocopherol and AD and MCI

Results from the meta-analysis indicate no differences in serum concentrations of serum γ-tocopherol between AD cases and healthy age-matched controls (SMD = −0.05, 95% CI −0.45 to −0.36; Z = 0.22, P =0.82) (**Figure 6**). There was heterogeneity amongst the serum level trials (Heterogeneity Tau^2 = 0.11; Chi^2 = 13.3, df=2 (p<0.001); 1^2 =85%).

Serum levels of γ-tocopherol were also not significantly different in MCI and age-related poor cognitive performance and MCI (SMD = −0.19, 95% CI −0.47 to −0.09; Z = 1.3, P = 0.19) (**Figure 7**). There was heterogeneity amongst the serum level trials (Heterogeneity Tau^2 = 0.04; Chi^2 = 6.37, df=2 (p<0.04); 1^2 =69%).

δ-tocopherol and AD and MCI

Results from the meta-analysis indicate no differences in serum concentrations of serum γ-tocopherol between AD cases and healthy age-matched controls (SMD = −0.17, 95% CI −0.54 to −0.88; Z = 0.47, P =0.64) (**Figure 8**). There was heterogeneity amongst the serum level trials (Heterogeneity Tau^2 = 0.37; Chi^2 = 40.58, df=2 (p<0.00001); 1^2 =95%).

Serum levels of γ-tocopherol were also not significantly different in MCI and age-related poor cognitive performance and MCI (SMD = −0.16, 95% CI −0.45 to −0.14; Z = 1.02, P = 0.31) (**Figure 9**). There was heterogeneity amongst the serum level trials (Heterogeneity Tau^2 = 0.05; Chi^2 = 7.17, df=2 (p<0.03); 1^2 =72%).

Discussion

This meta-analysis, based on the available data of case-control studies, provides evidence that patients with AD and age-related cognitive deficits have lower circulatory levels of α-tocophenol. Levels of the other tocopherols did not differ. These findings support some of the previous evidence on the potential association of vitamin E with AD.

Regarding possible mechanisms of how vitamin E might relate to AD and MCI, a number of studies have demonstrated the beneficial effects of vitamin E supplementation on various markers of inflammatory stress, cellular signalling and immune function in humans and its influence on AD-associated pathology [43]. It has been shown that vitamin E may be able to counteract oxidative stress induced by amyloid-β. For example, Yatin et al. demonstrated that vitamin E prevented amyloid-β1–42 induced protein oxidation, reactive-oxidative species production, and neurotoxicity in primary rat embryonic hippocampal neuronal culture, possibly through the scavenging of amyloid-β-induced free radicals [44]. The enzyme-inhibiting activity of various tocopherol isoforms also incorporate several AD-associated enzymes, including cyclo-oxygenases, which contribute to neuro-inflammation and oxidative stress [45]. The activity of both sub-groups have also been associated with reduced amyloid-β production through inhibiting secretase enzyme activity [46]. Similarly, vitamin E has been shown to confer a protective effect against hyper-phosphorylated tau protein [47]. Studies have also shown that vitamin E deficiency influenced gene expression in the hippocampus and in particular, the genes associated with hormones, nerve growth factor (NGF), apoptosis, dopaminergic neurotransmission, clearance of amyloid-β and advance glycated end products [48].

The APOE ε4 allele is associated with an increased risk of AD [18]. Interestingly, of those studies within this meta-analysis testing for APOE, there were less significant differences ($p=0.01$) in α-tocophenol levels between AD or MCI and control if APOE ε4 allele frequencies did not differ between the groups (**Supplementary Figure 2**). Previous research has shown a significant interaction between APOE genotype on AD progression with ε4 carriers declining faster than non-carriers following vitamin E and memantine treatment [49]. Possible mechanisms are that APOE may influence AD risk though its role in cholesterol transport, one consideration is that vitamin E and cholesterol share mechanisms of delivery to cells via LDL particles that genotype might influence [18].

Other factors may have also influenced these results and influenced vitamin E levels. Many of the studies did not account for nutritional status, energy intake and BMI. Nutritional status in older adults is an issue of increasing importance and malnutrition is associated with functional and cognitive decline in the demented elderly. One study has found antioxidants were lower in AD patients compared to the controls, that was suggested to be partly due to a different dietary intake of antioxidant nutrients [50]. Therefore, in such case-control studies, it is important to consider whether reductions in vitamin E may result from dietary changes in AD. This may also relate to BMI, though it is important to note that ten of the twenty-five studies found no differences in AD, only one reduced BMI. Detailed information on dietary intake might further have allowed to control whether reduced Vitamin E levels might have occurred through such dietary changes. As such, causal relationships between reduced serum tocopherol and AD cannot be determined due to the case-control nature of our study.

Not all studies controlled for the absence of supplement use, particularly vitamin E, among participants that might have been higher in control groups. Cigarette smoking, and high alcohol consumption, are important sources of reactive oxygen species (ROS), that overwhelm any protective effects associated with α-tocopherol levels. Lower levels of vitamin E have also been found in patients with alcoholism [51] and drug addiction [52]. These were not exclusion criteria in all studies.

Several prospective cohort studies have investigated plasma vitamin E levels and the subsequent risk of developing AD. While these provide limited evidence for the benefits of vitamin E supplementation, they nevertheless suggest that a high intake from dietary sources may confer some benefit in reducing the risk of developing AD compared to those with lower intake (for review see [43]). It is further suggested that neuroprotective effects may result from a combination of vitamin E isoforms rather than specifically to any individual congener [53]. However, there were only a limited number of studies that included β-, γ-, and δ-tocotrienols, in addition to α-, for this meta-analysis. *In vivo* studies have reported higher antioxidant activity of α-tocopherol compared to the other isoforms, and it has been suggested that α-tocopherol has a greater role in neuroprotection due to its relatively greater bioavailability and preferential retention by tissues [54]. However, it has also been suggested that its relative laboratory efficacy may be dependent upon experimental conditions [55]. Indeed, tocotrienols may exhibit more potent antioxidant activities than tocopherols [56].

Diet is an important source for tocopherols with α-tocopherol the major tocopherol in many edible oils as such as almond, peanut, olive, and sunflower oils. The content of γ-tocopherol in some edible oils such as canola, corn, camelina, linseed, soybean, and walnut oils are similar or higher than that of α-tocopherol (for review see [57]). Though some of the studies did control for extreme variances in diet however it cannot be discounted that variances in diet between AD patients and controls might have affected levels of the tocopherls [58]. A further consideration is that diet including intake of tocopherols [59] has been shown to influence gut microbiota, and gut microbiota has in turn been linked with AD [60].

In conclusion, this meta-analysis based on case-control studies demonstrates that serum vitamin E concentration is lower in patients with AD and poor cognition than in the age-matched controls. This suggests that low-serum vitamin E levels may be a risk factor for AD.

Acknowledgments

None.

Author contributions

SA, SB and CM designed the study. SA and CM performed the literature searches and data extraction. All authors contributed to the final version of the manuscript.

Conflict of interest

The authors report no conflicts of interest in this work.

This study did not receive any specific funding.

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Figures

Figure 1. Study Flow Diagram.

Figure 2. Standardized mean difference (SMD) and 95% confidence interval (CI) of serum α-tocopherol levels for AD and age-matched controls. Studies were sub-grouped dependent on if tocopherol levels were controlled for total cholesterol (TC) or not.

Figure 3. SMD and 95% CI of serum α-tocopherol levels for MCI and age-matched controls. Studies we sub-grouped dependent on if tocopherol levels were controlled for TC or not.

Figure 4. SMD and 95% CI of serum γ-tocopherol levels for AD and age-matched controls.

Figure 5. SMD and 95% CI of serum γ-tocopherol levels for MCI and age-matched controls.

Figure 6. SMD and 95% CI of serum β-tocopherol levels for AD and age-matched controls.

Figure 7. SMD and 95% CI of serum β-tocopherol levels for MCI and age-matched controls.

Figure 8. SMD and 95% CI of serum δ-tocopherol levels for AD and age-matched controls.

Figure 9. SMD and 95% CI of serum δ-tocopherol levels for MCI and age-matched controls.

Table 1. *Characteristics of studies focusing on AD included in the meta-analysis.*

Study	Location	Design	Subjects (n) (cases; controls)	Females (%) (cases; controls)	Age (yrs) (cases; controls)	Case criteria	Exclusion criteria	Controlled for AD-associated risk factors and diet	Tocopherol Measurement	Controlled for cholesterol
Zaman 1992 [36]	UK	CC	20;10	matched	83; 80	Hachinski's ischaemic score and CT brain scanning	Dis: hypothyroid-ism, low vit.B12, depression, intracranial lesions Drugs: - Med: - Diet: -		Blood	No
Ahlskog 1995 [61]		CC	12;15	66; 80	73.8 (57-88); 61.4 (46-85)	DSM-III-R, NINCDS-ADRDA	Dis: DM, VD, major organ failure; rheumatologic disease; infection, cancer, Drugs: - Med: aspirin, nonsteroidal antiinflammatory, corticosteroids, immunosuppressives in prior week Diet: malnutrition.		Morning, Fasted, serum.	No
Jimenez-Jimenez 1997 [62]	Spain	CC	44;37	43.18; 45.9	72.5±8.6; 70.1±7.2	DMS-IV, MMSE<23	Dis: chronic hepatopathy, malabsorption diseases, severe systemic disease, Drugs: Alcoholism (>80 g/day in the last 6 mths) Med: drugs which modify lipid absorption, Diet: Atypical diets, vit.sup. therapies	AD- ↓ BMI	Fasted, serum.	Yes

Aejmelaeus 1997 [37]	Finland		22:14		85.5; 77.3	NINCDS-ADRDA	Dis: Any major medical illness Drugs: smokers. Med: prescription drugs Diet: AD-standardized hospital food. Vitamins, malnutrition			No
Sinclair 1998 [21]	UK	CC	25;41	40; 58	74.3 ± 8.1; 73.4 ± 7.2	NINCDS-ADRDA	Dis: major medical illness, DM Drugs: Med: medication known to affect markers of oxidative stress (apart from aspirin); Diet: malnourishment, abnormal BMI	Diets - one main meal daily, include fresh fruit or vegetables; Smoking (4% AD; 7% con)	Morning.	Yes
Foy 1999 [22]	Ireland	CC	79;58	38;44.8	72–83; 69–80 IQ range	NINCDS-ADRDA, DSM-IV	Dis: major medical illness, DM, blood test to exclude secondary causes of dementia and brain CT scan Drugs: Med: Diet: three meals a day, include meat and vegetables, vitamins		Plasma.	Yes
Feillet-Coudray 1999 [25]	France	CC	25;14	72; 57	75 ± 1; 76 ± 1	DSM-IV	Dis: Inflammatory diseases, DM, Drugs: smoking Med: estrogen replacement therapy, Diet: vitamins		Morning, Fasted, plasma.	Yes
Schippling 2000 [63]	Germany	CC	29;29	51.7; 57.7	71.1±10.1; 55.1±18.8	NINCDS-ADRDA, DSM-IV	Dis:- Drugs: - Med: - Diet: good general nutritional state, antioxidant supplements	AD – ↑ ApoE ε4, ↓ smoking. No diff CHD, hypertension, DM, plasma lipids	Morning,.Fasted, serum or plasma	Yes
Bourdel-Marchasson 2001 [64]	France	CC	20;23	80; 69	80 ± 6; 76 ± 7	NINCDS-ADRDA, DSM-3R	Dis: DM and other diseases in prior 2mths Drugs: smoking; Med:drugs	No diff BMI, and energy intake, proteins, fat,	Morning, plasma.	No

							Diet: vit.A, E or C, weight instability	alcohol and micronutrients.		
Polidori 2002 [38]	Germany	CC	35;40		85.9 ± 5.5; 85.4 ± 4.4	NINCDS-ADRDA	Dis: Anxiety/ depression, major organ failure. Blood test to exclude secondary causes of dementia. Drugs: smoking, alcohol abuse Med: - Diet: malnutrition, dyslipidemia, alteration of protein metabolism. iron or antioxidant supplements	no diff yrs education, BMI, MNA, biochemical indexes of nutritional status, dietary intake.		No
Mecocci 2002 [65]	Italy	CC	40;39	50;52.5	74.8	*DSM IV-R*13 and of NINCDS-ADRDA	Dis: - Drugs: - Med: - Diet: -	No diff BMI, plasma albumin & transferrin, MNA, dietary habits	Plasma	No
Rinaldi 2003 [39]	Italy	CC	63;56	73; 64.3	75.8 ± 7.2; 76.8 ± 6.9	MCI; CDRAD; NINCDS-ADRDA	Dis: Anxiety/depression, major organ failure, Drugs: smoking, alcohol abuse, Med: - Diet: malnutrition, dyslipidemia, alteration of protein metabolism, iron or antioxidant supplements	no diff yrs education, BMI, MNA, Biochemical indexes of nutritional status and dietary intake. no influence of ApoE ε4 on peripheral antioxidants status	Plasma.	No
Polidori 2004 [66]	German	CC	63;55	73;65	76.8±6.9;	NINCDS-ADRDA	Dis: Anxiety/depression, major organ failure. Blood test to exclude secondary causes of dementia. Drugs: smoking, alcohol abuse	no diff yrs education, BMI, MNA, Biochemical indexes	Plasma.	No

							Med: - Diet: malnutrition, dyslipidemia, alteration of protein metabolism. iron or antioxidant supplements	of nutritional status and dietary intake.		
Engelhart 2005 [28]	Netherlands	CS	65;437	60; 59	83.7 ± 7.1; 71.9 ± 6.7	NINCDS-ADRDA and DSM-3R	Dis: - Drugs: current smokers Med: - Diet: -	No diff TC, yrs education, BMI.	Morning, fasted, plasma	No
Mas 2006 [67]	France	CC	100; 186	61; 59.67	73.52± 9.06; 74.71± 10.88	DSM-IV and NINCDS-ADRDA	Dis: Drugs: Med: hypocholesterolemic drugs Diet: vitamin supplements	AD - ↑ Apo ε4 No diff TC	Fasted, serum.	Yes
Ciabattoni 2007 [29]	Italy	CS	44; 44	56.8; 61.4	73 ± 8; 75 ± 7	NINCDS-ADRDA	Dis: acute infectious or inflammatory disease, cancer, chronic hepatic disease, psychiatric, neurologic, CVD Drugs: alcohol abuse, Med: Diet: antioxidant vitamins.	No diff in BMI, yrs education, hypercholesterolemia, diabetes, smoking status, and arterial hypertension	Fasted, serum, TC, α-TOH	Yes
Baldeiras 2008 [40]	Portugal	CC	42; 37	83.9±7.2; 73.7±6.1	73.0 ± 1.2; 68.4 ± 1.8	Mild AD: DSM-IV-TR	Dis: Drugs: Med: Diet:	↑ APOE ε4 No diff yrs education, biochemical indexes of nutri-tional status, BMI	AM, fasted, plasma	No
Mangialasche 2010 [53]	Finland	CS	57; 145	84; 78	86.2± 2.8; 84.6±3.2	NINCDS-ADRDA	Dis: - Drugs: - Med: - Diet: -	No diff yrs education, *APOE* ε4, BMI, TC, presence of multi-morbidity and	Plasma.	Yes

								disability at, smoking status, alcohol use, vitamin supplements		
Iuliano 2010 [13]	Italy	CC	37;24	73; 62.5	76.03±7.9; 69.83±6.4	AD; NINCDS-ADRDA	Dis: major medical ill- nesses, DM, hematological/oncological disorders; vitamin B12 or folate deficiency, pernicious anemia; gastrointestinal, renal, hepatic, endocrine or cardiovascular system diseases; newly treated hy-pothyroidis; psychiatric disorders; MRI imaging Drugs: alcoholism, drug abuse during Med: antioxidants,hypolipemics Diet:	AD – ↓ yrs education	Morning, fasted, serum or plasma.	Yes
Mangialasche 2012 [14]	Europe	CS	168; 187	68; 54	77.4±6.3; 74.7±5.3	DMS-IV.	Dis: psychiatric disorders illness, systemic disease/organ failure, Drugs: alcoholism, drug abuse Med: Diet:	AD - ↓ yrs education, ↑ *APOE* ε4	Fasted, serum.	Yes
Giavarotti 2013 [68]	Brazil	CC	23;42	ND	82	MMSE, CDR	Dis: CVD, cancer, inflammatory diseases, high CRP. Drugs: Med: Diet:		Fasted, plasma	Np
Mangialasche 2015 [41]	Italy	CC	28; 21	53.6; 52.4	74.9 ± 6.9; 79.1 ± 7.7	AD: NINCDS-ADRDA and DSM-IV	Dis: blood test to exclude secondary causes of dementia Drugs: Med: Diet:	AD - ↓ yrs education, ↑ *APOE* ε4	Fasted, plasma.	No
Raszewski 2016 [42]	Poland	CC	31; 40		77.3 ± 6.8;	NINCDS-ADRDA	Dis: hypercholesterolaemia, hypertension,	AD - ↓ TC	Morning,	Yes

					73.6 ± 9.4	and DSM-IV	DM, metabolic syndromes, psychiatric disorders Drugs: Med: Diet:	No diff in yrs education	fasted, serum.	
Mullan 2017 [69]	Ireland	CC	251; 308	64; 61	80.2±7.7; 76.5±6.7	NINCDS, ADRDA.	Dis: history of other neurological disorders. Drugs: - Med: - Diet: -	AD - older, ↑ APOE ε4, ↓ yrs education, ↓ blood pressure No diff smoking, DM, hypertension, CVD, Hypercholesterolemia, Aspirin/clopidogrel	Serum.	Yes

CC, case-control; CS, cross-sectional, blood test to exclude secondary causes of dementia (included measurements of vitamin B 12, folic acid and thyroid hormones); Dis., disease; Med., medications; CVD, cerebrovascular disease; VD, vascular disease; BMI, body mass index; DM, diabetes mellitus; MNA, Mini Nutritional Assessment; MMSE, Mini Mental State Examination

Table 2. *Characteristics of studies focusing on Age-related poor cognitive function included in the meta-analysis.*

Study	Location	Design	Subjects (n) (cases; controls)	Females (%) (cases; controls)	Age (yrs) (cases; controls)	Case criteria	Exclusion criteria	Sig differences in MCI and diet-related factors.	Tocopherol Measurement	Controlled for cholesterol
Schmidt 1998 [30]	Austria	CS	1769	58.3	62.0± 6.3	MDRS score: poor cognitive function if in lowest 25^{th}	Dis: neuropsychiatric disease, CVD, dementia,	Cases - ↓ yrs education, ↑ arterial hypertension	Plasma.	No

						percentile of results	abnormal neurological exam. Drugs: - Med: - Diet: Regular vitamin intake			
Ortega 2002 [27]	Spain	CS	120		65-91	PMSQ scores 3 categories of results	Dis: major underlying illness, abnormal hepatic function, DM, endocrine disorders, serious mental deterioration Drugs: Med: medication that might modify results Diet: weight gain/loss diets	No sig diff in weight, height, BMI, smokers, supplements	Fasted, serum.	No
Rinaldi 2003 [39]	Italy	CC	25;56	56; 64.3	75.8 ± 4.8; 75.8 ± 7.2	CDRAD; NINCDS-ADRDA	Dis: Anxiety/depression, major organ failure, blood test to exclude secondary causes of dementia Drugs: smoking, alcohol abuse, Med: Diet: malnutrition, dyslipidemia, alteration of protein metabolism, taking iron or antioxidant supplements.	MCI - ↑ APOE ε4 No diff in yrs education, BMI, MNA, Biochemical indexes of nutritional status and dietary intake.	Plasma	No
Engelhart 2005 [28]	Netherlands	CS	65;437	64; 59	83.7 ± 7.1; 71.9 ± 6.7	Cognitive decline; MMSE	Dis: Drugs: Med: Diet:		Morning, fasted, plasma	No
Ravaglia 2008 [15]	Italy	CS	52; 666	76.7; 53.4	83.9± 7.2; 73.7± 6.1	MMSE <24; dementia: clinical diagnosis according to DMS-IV	Dis: - Drugs: - Med: - Diet: -	No diff in yrs education, APOE ε4, smoking, CVD, Stroke, Sedentary lifestyle, BMI, TC, Mediterranean Diet score	Fasted, serum.	Yes

Baldeiras 2008 [40]	Portu gal	CC	85; 37	56.5; 73	71.1± 0.8; 68.4± 1.8	MCI; MMSE, amnestic, multiple-domain, 0.5 in Clinical Dementia Rating Sale (CDR)	Dis: biochemical, neurological and neu-ropsychological evaluation Drugs: Med: Diet:	No diff APOE ε4, yrs education, biochemical indexes of nutritional status, BMI, smoking	Morning, fasted, plasma	No
Iuliano 2010 [13]	Italy	CC	md-MCI 29; 24: a-MCI 24; 24	md-MCI 73; 62.5: a-MCI 73; 62.5	md-MCI 70.86 ±6.6; 69.83 ±6.4: a-MCI 68.42 ±5.4; 69.83 ±6.4	md- MCI; CDR ,a-MCI	Dis: major medical ill-nesses, DM, hematological/oncological disorders; anemia; gastrointestinal, renal, hepatic, endocrine or cardiovascular system diseases; newly treated hy-pothyroidis; psychiatric disorders; MRI abnormalities, Drugs: alcoholism, drug abuse; Med: antioxidants, hypolipemics Diet: vitamin B12 or folate deficiency, pernicious		Morning, fasted, serum or plasma.	Yes
Mangialasche 2012 [14]	Europe	CS	168; 187	68; 54	77.4± 6.3; 74.7± 5.3	MMSE <24;	Dis: psychiatric disorders illness, systemic disease/organ failure, Drugs: - alcoholism, drug abuse Med: - Diet: -	MCI - ↓ yrs education, ↑ *APOE* ε4	Fasted, serum.	Yes
Johnson 2013 [31]	USA	CS	148; 150	84.5; 73.3	99.7± 4.6; 93.3± 8.3	MMSE	Dis: - Drugs: - Med: - Diet: -	Institutionalized – ↑ females, ↑ nonsmokers, older, ↓ yrs education, ↓ alcohol use, ↓ BMI. No diff hypertension	Fasted, serum.	Yes

Mangialasche 2013 [32]	Finland	CS	64; 76	76; 68	71.5± 3.8; 71.3± 4.0	MMSE <24	Dis: - Drugs: - Med: - Diet: -	no diff ApoE ε4, BMI, serum cholesterol, CVD, stroke DM	Fasted, serum.	Yes
Mangialasche 2015 [41]	Italy	CC	28; 21	54.5; 52.4	76.5 ± 6.6; 79.1 ± 7.7	MayoClinic Research Center Criteria.	Dis: blood test to exclude secondary causes of dementia. Drugs: - Med: - Diet -	MCI - ↓ yrs education, ApoE ε4	Fasted, plasma.	No
Yuan 2016 [35]	China	CS	138; 138	65;65	64.71 ± 0.52; 64.23 ± 0.47	MoCA and CDR	Dis: Illnesses known to affect oxidative stress or cognitive function, CVS, stroke, Drugs: alcoholism Med: antioxidant supplements, antidepressants, CNS medications Diet: -	MCI - ↓ yrs education, ↓TC, ↓ LDL-C, ↓HDL-C, ↓ fish, ↑ red meat consumption. No diff BMI	Fasted, plasma.	Yes
Huang 2018 [33]	China	CS	583; 1171	67.6	65.3± 6.3	MoCA	Dis: Illnesses known to affect oxidative stress or cognitive function, CVS, stroke, Drugs: alcoholism Med: antioxidant supplements, antidepressants, CNS medications Diet: -	MCI - ↑serum glucose, ↑TC, ↑HDL-C, ↓ LDL-C, ↓vegetable and ↑grain intake. No diff ApoE ε4	Fasted, serum.	Yes

CC, case-control; CS, cross-sectional, blood test to exclude secondary causes of dementia (included measurements of vitamin B 12, folic acid and thyroid hormones); Dis., disease; Med., medications; CVD, cerebrovascular disease; VD, vascular disease; BMI, body mass index; DM, diabetes mellitus; MNA, Mini Nutritional Assessment; MMSE, Mini Mental State Examination